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10/568,745	02/21/2006	Mitsuko Ideno	1422-0709PUS1	6655

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EXAMINER	
SKELDING, ZACHARY S	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/568,745	IDENO ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009 and 14 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *14,17-19 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,16,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6-3-09, 2-29-08, 1-3-08, 8-23-07, 11-30-06, 5-23-06, 2-21-06.

DETAILED ACTION

1. Applicant's election with traverse of group I, wherein the species of fibronectin fragment is SEQ ID NO: 13 and wherein the method includes a step of diluting a cell culture solution in the replies filed August 10, 2009 and August 14, 2009 are acknowledged.

   The traversal is on the ground(s) that at SEQ ID NOs: 9-20 and 25 should be examined contemporaneously because "these sequences share a common special technical feature and structure, i.e., a cell adhesion activity and/or a heparin binding activity, as specified in claim 11".

   This is not found persuasive because some of the fibronectin fragments of SEQ ID NOs: 9-20 and 25 share neither a common special technical feature nor a common structure. For example, the fibronectin fragments of SEQ ID NO: 9 lacks the heparin-binding domain structure and activity while the fibronectin fragments of SEQ ID NO: 11 has the heparin-binding domain structure and activity but lacks the cell adhesion structure and activity. Moreover, many of the claims under examination merely recite "fibronectin or a fragment thereof" which based on the principal of claim differentiation encompass in their breadth fragments of fibronectin NOT having cell adhesion activity and NOT having heparin binding activity.

   The requirement is still deemed proper and is therefore made FINAL.

   Claims 1-24 are pending.

   Claims 1-13, 15, 16, 20 and 21 are under examination wherein the elected species of fibronectin fragment is SEQ ID NO: 13 and wherein the method includes a step of diluting a cell culture solution.

   Claims 14, 17-19 and 22-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected Group or species of invention.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   A) Claim 1 and dependent claims thereof are indefinite in the recitation of the "induction" of a cytotoxic lymphocyte. For example, are the claims intended to encompass differentiation

of a cytotoxic lymphocyte? If so, it is unclear how a cytotoxic lymphocyte can be differentiated (i.e. induced) from itself (i.e. by inducing a cytotoxic lymphocyte).

B) Claim 8 is indefinite in the recitation of "and the cell culture carrier…" in that parent claim 7 recites "or a cell culture carrier…" and it is unclear if claim 8 requires both cell culture equipment AND a cell culture carrier or if it meant to further specify the alternative recitations of claim 7.

C) Claim 3 and dependent claims thereof are indefinite in the recitation of a cytotoxic lymphocyte containing "CD8-positive cell in a higher ratio". While a population of cells might contain a higher ratio of CD8+ cells than another population of cells, it is unclear how a cytotoxic lymphocyte itself can contain a higher ratio of CD8 positive cells, as claimed.

D) Claim 4 and dependent claims thereof are indefinite in the recitation of an "expansion fold" of the cytotoxic lymphocyte being high compared to the method of preparing a cytotoxic lymphocyte in the absence of fibronectin. It is not clear if the claim requires that the cytotoxic lymphocyte actually expand as a result of the claimed method, or whether "expansion fold" refers to a property of the cytotoxic lymphocyte (i.e. an increased potential for expansion). In other words, what is the meaning of "an expansion fold"?

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of fibronectin "fragments", or polypeptides having a "substitution, deletion, insertion, or addition to one or more amino acids" of a fibronectin fragment.

The instant claims encompass employing a genus of fibronectin "fragments" in the claimed method. Fibronectin is a large polypeptide comprising several different domains, including type I, type II, and type III homology repeats. Thus, the instant claims encompass structurally different fibronectin fragments comprising different amino acids sequences corresponding to different fibronectin domains. Additionally, there is no limitation that the claimed fragments even function to stimulate cytotoxic lymphocytes. Indeed, the claims might encompass a fibronectin fragment comprising only 2 amino acids of fibronectin. Likewise, the claims encompass polypeptides comprising a "substitution, deletion, insertion, or addition to one or more amino acids" of the claimed fragments. Said polypeptides would comprise different

structures, owing to their unique amino acid sequence. Furthermore, the only functional limitation of the mutated fragments is that they have a "function equivalent" to that of the polypeptides of the claims. However, the claims do not describe what "function" is required. For example, any polypeptide might function as an antigen. Therefore, the claims might encompass mutated polypeptide fragments that are functional equivalents of an antigen. In contrast to the broad range of structurally and functionally different fragments encompassed by the claims, the instant specification only discloses fragments of the type III region of fibronectin. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

6. Claims 1-13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing cytotoxic lymphocytes comprising culturing peripheral blood mononuclear cells in the presence of fibronectin or a fibronectin fragment comprising SEQ ID NO: 13 does not reasonably provide enablement for a method for preparing cytotoxic lymphocytes comprising culturing peripheral blood mononuclear cells in the presence of any fragment of fibronectin, including fibronectin fragments having a substitution, deletion, insertion, or addition to one or more amino acids.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

With regards to the instant claims, their breadth comprises a primary issue as regards the unpredictability of the claimed method. The claims encompass preparing cytotoxic lymphocytes with increased cytotoxic activities, expression of IL-2 receptor, expansion fold,

or CD8 ratio comprising inducing, maintaining, or expanding said lymphocytes in the presence of any fibronectin fragment. Fibronectin is 250kDa polypeptide consisting of repeating homology units termed type I, type II, and type III repeats (see Kornblihtt et al., 1996, cited on an IDS, page 248 in particular). It is known that the cell binding and heparin binding domain comprising type III repeats are important in the ability of fibronectin to participate in cell adhesion and growth (see Yoneda et al., 1995, cited on an IDS, page 169-170). However, other fibronectin domains, including the type I repeats, are functionally distinct. For example, some type I domains are involved in binding to the clotting factor fibrin (see Rostagno et al., 1999, cited on an IDS, Abstract). It is not clear how said type I fragments could be used to prepare cytotoxic T cell lymphocytes with increased cytotoxic activity, expression of IL-2 receptor, expansion fold, or CD8 ratio, as is encompassed by the instant claims. Additionally, the instant claims encompass employing fibronectin fragments comprising a substitution, deletion, insertion, or addition to one or more amino acids. The only functional limitation of said fragments is that they be "functional equivalents". However, the claims do not specify what function they are required to be equivalent with. For example, the claims might encompass mutated fragments that "function" as an antigen. Thus, the claims might encompass employing any substitution, deletion, or addition, to any amino acid of the claimed fragments, including to regions known to be critical to the function of fibronectin for increasing cytotoxic activity of T cells (for example, the RGD region, see Ostergaard et al., 1995, cited on an IDS, Abstract). Thus, given the state of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. However, the specification only provides examples utilizing type III fibronectin fragments from the cell binding or heparin binding domain of the polypeptide. Furthermore, the only disclosure of a fragment is a single methionine addition linking various type III fibronectin fragments. This is not commensurate in scope with the instant claims which encompass preparing cytotoxic lymphocytes with any fibronectin fragment, or any substation, addition, or deletion to said fragments. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 102(b) as being unpatentable over Lamers et al. (Cancer Gene Therapy (2002) 9, 613–623) as evidenced by the teachings of the instant specification at pages 12-13 and 188 and the Examples at pages 55-125.

Lamers teaches a method for preparing cytotoxic lymphocytes comprising carrying out at least one step selected from induction, maintenance and expansion of a cytotoxic lymphocyte using a medium containing serum and plasma at a total concentration of 0% by volume or

more and less than 5% by volume, in the presence of fibronectin, a fragment thereof or a mixture thereof (see page 615, right col. 2nd paragraph to page 616, column bridging paragraph).

In performing this method Lamers teaches the use of CH-296 fibronectin containing a heparin-binding domain immobilized on a cell culture bag (see ibid), as evidenced by the instant specification "CH-296" = SEQ ID NO: 13 = FERM BP-2800 disclosed, e.g., in Taguchi et al., 5198423, cited on an IDS. Moreover, as evidenced by the instant specification at page 12-13 and 188, CH-296/SEQ ID NO: 13 comprises a number of the fibronectin fragments recited claim 10 (see ibid).

Furthermore, Lamers teaches incubating PBMC in the culture bag with fibronectin and a retroviral transduction vector at an initial concentration falling within the range recited in claim 13 and a step of diluting the cell culture solution, step of exchanging the medium, or step of exchanging the cell culture equipment, wherein the culture conditions immediately after at least said step of diluting the cell culture solution, step of exchanging the medium, or step of exchanging the cell culture equipment satisfy the conditions of having a concentration of cells in the cell culture solution falling within the range recited in claim 15 or a serum/plasma concentration recited in claim 16 (see ibid).

With respect to the limitations of claims 2-5, 9 and 11, in following the teachings of Lamers one of ordinary skill in the art would necessarily produce cytotoxic lymphocytes that highly expresses an interleukin-2 receptor as compared to a cytotoxic lymphocyte prepared in the absence of fibronectin; produce cytotoxic lymphocyte contains CD8-positive cell in a higher ratio as compared to a cytotoxic lymphocyte prepared in the absence of fibronectin; enhance cytotoxic activity or maintain high cytotoxic as compared to a cytotoxic activity of a cytotoxic lymphocyte prepared in the absence of fibronectin; produce lymphokine-activated killer cells as evidenced by the teachings of the instant specification examples at pages 55-125.

Thus, Lamers anticipates the claimed method.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-13, 15, 16, 20 and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8, 15-18, 28, 30, 32, 34, 36, 37 and 38 of copending Application No. 10/486,512 (20050042208, cited on an IDS) in view of Lamers et al. (Cancer Gene Therapy (2002) 9, 613–623).

The '512 application claims a method for inducing cytotoxic T cells, a method for maintaining cytotoxic T cells, and a method for expanding cytotoxic T cells comprising incubating said T cells with fibronectin or a fragment thereof. The '512 application further claims that said fragment comprises at least one of a VLA-4, VLA-5, and a heparin binding domain.

The reference claims differ from the instant claims in that they do not recite using a medium containing serum and plasma 0-5% by volume or the limitations of the instant claims where the concentration of cells is between 1-5 x 10^5 cell/cm2, or transfecting the cytotoxic T lymphocyte with a foreign gene, or diluting the cell culture solution.

However, each of these limitations would have been obvious to one of ordinary skill in the art in view of the teachings of Lamers that transfection with an T cell specific antibody fusion protein allows for the production of potent cytotoxic T cells, that concentrations of cells between 1-5 x 10^5 cell/cm2 can be productively used to prepare said potent cytotoxic T cells, and that RPMI supplemented with 2% HSA was as potent as RPMI supplemented with 10% FCR or human serum (see Lamers ibid as well as page 621, left col. 1st paragraph). As would be obvious to one of ordinary skill in the art as taught by Lamers RPMI/HSA is the best choice for clinical use because it has been approved for such a purpose.

This is a provisional obviousness-type double patenting rejection.

11. Claims 1-13, 15, 16, 20 and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 10, 12, 28, 29, 31-35 and 37-39 of copending Application No. 10/509,055 (20050227354, cited on an IDS).

The '055 application claims a method for preparing a cytotoxic lymphocyte comprising the step of carrying out at least one step selected from induction, maintenance, and expansion of a cytotoxic lymphocyte in the presence of the fibronectin fragment of SEQ ID NO: 13. The '055 application also claims that the fibronectin is immobilized on a substrate, that the

concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml, and that the method includes transduction with a retrovirus.

The reference claims differ from the instant claims in that they do not recite using a medium containing serum and plasma 0-5% by volume.

However, this limitation would have been obvious to one of ordinary skill in the art in view of the teachings of Lamers that RPMI supplemented with 2% HSA was as potent as RPMI supplemented with 10% FCR or human serum (see Lamers ibid as well as page 621, left col. 1st paragraph). As would be obvious to one of ordinary skill in the art as taught by Lamers RPMI/HSA is the best choice for clinical use because it has been approved for such a purpose.

This is a provisional obviousness-type double patenting rejection.

12. Claims 1-13, 15, 16, 20 and 21 are directed to an invention not patentably distinct from claims 1, 8, 15-18, 28, 30, 32, 34, 36, 37 and 38 of commonly assigned Application No. 10/486,512 or claims 1-3, 5-7, 10, 12, 28, 29, 31-35 and 37-39 of commonly assigned Application No. 10/509,055 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). The commonly assigned applications discussed above would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned cases qualify as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644